Remarks

Claims 9, 10, 39, and 47-59 are pending. Of these, claims 47, 57 and 59 have been amended hereinabove, and claim 51 has been canceled without disclaimer or prejudice to applicants' right to pursue the subject matter previously claimed in the future. All of the amendments have been made to more particularly point out and distinctly claim subject matter which applicants regard as a patentable invention. All of the amendments are fully supported by the specification and none involve the introduction of new matter into the claims. Accordingly, entry of these amendments is requested.

As previously pointed out, important aspects of applicants' invention which differentiate their invention from the prior art include the following:

a. use of three or more stains, two or more of which are used to differentially define subcellular compartments;
b. localization and quantitation analysis is done with the use of an upright or inverted optical microscope rather than a confocal microscope;
c. localization and quantitation analysis is done on cells within a tissue sample;
d. assigning pixel locations to two or more alternative subcellular compartments;
e. reiteratively analyzing and reassigning pixel locations to subcellular compartments based upon relative intensity values of the stains; and

f. effecting both localization and quantitation of a biomarker of interest within one subcellular compartment relative to another subcellular compartment based on the total stain intensity at pixel locations assigned to such subcellular compartments.

Turning now to the November 24, 2006 Final Office Action, applicants are pleased to note that the Examiner has found applicants' arguments and amendments filed August 31, 2006 persuasive and has withdrawn the rejections made in previous office actions.

Claim Objections

In response to the Examiner's objection to claims 47, 57, and 59 for containing periods within the claim, applicants have amended these claims to delete the offending periods. Applicants understand that so amended these claims are no longer subject to objection by the Examiner.

Claim Rejections - 35 U.S.C. §112, 2nd paragraph

In response to the Examiner's rejection of the claims as being indefinite in paragraphs 3, 4 and 5 of the Office Action, applicants have amended claims 47 and 59 to recite each image comprises 1024 x 1024 pixel locations, thereby incorporating into claims 47 and 59, now canceled claim 51, which recited the high resolution image comprises 1024 x 1024 pixel locations. Although applicants disagree that the term "high resolution" was indefinite when interpreted in light of the specification,

applicants maintain that as amended, claims 47 and 59 are no longer subject to rejection on the basis of any indefiniteness in the term high resolution.

In response to the rejection in paragraphs 3, 4, 6, 7 and 8 of the Office Action of the claims as being indefinite, applicants have amended claim 59. The amendments include, inter alia, (a) the deletion of the phrase "to assess spillover" as superfluous since the recited step of "reiteratively analyzing..." is sufficient without the offending phrase; (b) replacement of the phrase "the other compartment" with the phrase "each of the first compartment and the second compartment"; and (c) replacing the phrase "first to second compartment intensity" with the phrase "the first stain intensity relative to the second stain intensity." Based on these amendments, applicants maintain that claim 59 is no longer subject to rejection on the basis of any indefiniteness for the reasons set forth in paragraphs 6, 7, and 8 of the Office Action.

Accordingly, applicants request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. §112, 2nd paragraph.

Claim Rejections - 35 U.S.C. § 103

In paragraphs 10[1] and 11 of the Office Action, the Examiner has rejected all of the pending claims except claims 54-56 and 58 under 35 U.S.C. §103(a) over Staines et al. in view of Wood et al.

[1] Applicants note there is no paragraph 9 in the Office Action.

In paragraph 12, the Examiner has rejected all of the pending claims except claim 58 under 35 U.S.C. §103(a) over Staines et al. in view of Wood et al further in view of Forus et al.

In paragraph 13, the Examiner has rejected all of the pending claims except claims 54-56 over Staines et al. in view of Wood et al. further in view of Harris et al.

Before discussing the references in detail, applicants wish to point out that neither Staines et al., the Examiner's primary reference, nor Wood et al., the Examiner's secondary reference, in each of the three rejections set forth in paragraphs 10-13 of the Office Action, disclose any of the following elements of applicants' claimed invention:

a. subcellular compartments at all in tissue sections[2];
b. marker defined two or more subcellular compartments;
c. two different stains specific for the two different subcellular compartments;
d. assigning pixel locations as between two or more alternative subcellular compartments;
e. reiteratively analyzing and reassigning each pixel

[2] Applicants note that the Examiner's statement on page 4, bottom paragraph, that he interprets compartments to include anything from an organelle to a biomolecule or ion. However, the claims recite "subcellular compartment," the meaning of which is well established and known in the art to mean a structural or biochemical portion of a cell that is separated from the rest of the cell (See, for example, PDR Medical Dictionary, Second Edition (2000), p. 387, a copy of which is attached hereto as **Exhibit A**). Moreover, the phrase "subcellular compartment" must be interpreted consistently with the use of the term in the application. See, for example, claim 9. Thus, there is no basis for the Examiner's interpretation that a subcellular compartment may be an ion such as, for example, Na^+, K^+, or Cl^- or a biomolecule such as ATP.

location as between subcellular compartments based on relative stain intensities;

f. analyzing an image of a stain specific for a biomarker at the pixel location assigned to each of the subcellular compartments so as to localize the biomarker as between subcellular compartments; and

g. determining the total intensity of the third stain at the pixel locations assigned to the subcellular compartments so as to quantitate the amount of the biomarker present therein.

Thus, a combination of the teachings of Staines et al. and Wood et al. does not result in a method having all the elements claimed. Accordingly, even if it were obvious to combine the teachings of these references (which applicants maintain would not be true) the result would not be the applicants' claimed invention.

With specific reference to Staines et al., applicants note that Staines et al. do not disclose a method for either localizing or quantitating a biomarker within a cell, and certainly not within a subcellular compartment. Staines et al. disclose a method for localizing a biomarker at the level of the cell soma and within terminal regions (see abstract, right hand column, lines 3-4), within the brain and peripheral tissue (see page 145, 2nd line from the bottom). The specific observation reported by Staines et al. (page 148) concern the pancreas, the medullary Raphe

nucleus[3], the cortex and hippocampus, and the paraventricular nucleus[3]. Thus, Staines et al. are staining at the cellular, not the subcellular, level. In addition, Staines et al. do not measure one stain within an area defined by another stain, let alone one stain (for the biomarker) within two areas defined by two area specific stains. Moreover, the method of Staines et al. is not pixel location based but based on photographs and is not computer implemented. Finally, as noted above, Staines et al. do not disclose any of the recited elements identified as a) through g) earlier in this discussion of the §103(a) rejections.

With specific reference to Wood et al., once again the method is not applied at the subcellular level. Wood et al. is localizing a biomarker within regions of muscle (see Abstract, left hand column, seventh line from the bottom). As a result, Wood et al. do not use stains to label a subcellular compartment let alone two stains specific for two different subcellular compartments. In fact, Wood et al. only employ two stains in total which is not sufficient to localize a biomarker in one subcellular compartment as opposed to another subcellular compartment. Moreover, the localization of Wood et al. employs a confocal microscope, not an optical microscope (see page 677, right hand column, second complete paragraph). Finally, as noted above, Wood et al. do not disclose any of the recited elements identified as a) through g) earlier in this discussion of the §103(a) rejection.

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[3] Applicants note that the Examiner, on page 6 of the Office Action, referring to claim 9, appears to have mistaken the word nucleus in Staines et al. as referring to the nucleus of a cell, i.e. a subcellular compartment. The "nucleus" of Staines et al. is a region within which neurons are present.

Based on the preceding comments, no combination of Staines et al. and Wood et al. (not even one based on the impermissible use of hindsight) results in a method having all of the elements recited in applicants' independent claims 47 and 59. Therefore, these claims are not properly rejected under §103(a). Moreover, neither of the tertiary references cited by the Examiner, Forus et al. or Harris et al., disclose the missing elements.

With specific reference to Harris et al., the staining taught is done using cells or cells harvested from tissue, not in tissue sections and requires the use of a confocal microscope. Harris et. al. do not measure one stain within two areas much less in two areas defined by two subcellular compartment specific stains.

With specific reference to Forus et al., the method is not applied to tissue sections and offers no teaching with regards to the other elements recited in the applicant's claims that are also not provided by Staines et. al., Wood et. al. or Harris et. al.

Since no combination of Staines et al. and Wood et al. nor these references in view of Harris et al. and Forus et al., disclose all the elements of independent claims 47 and 59, the combination of these references cannot render obvious any of the dependent claims which recite elements in addition to those recited in the independent claims. Therefore, a detailed discussion of the rejections as applied to the dependent claims

is not presented. However, the following comments are made:

1) As to claim 9, Staines et al. do not show the subcellular compartment is a nucleus. This is a misinterpretation of the word "nucleus" in Staines et al.
2) As to claim 49, Wood et al. do not teach regions not assigned to one of two subcellular compartments are assigned to a third subcellular compartment.
3) As to claim 67, there is no claim 67.
4) As for claim 52, once again, Staines et al. do not disclose a nucleus within a cell; Wood et al. do not have a page 150 and do not disclose localization to a membrane within a cell.
5) As for claim 57, Wood et al. do not disclose a method for subtracting out of focus elements as recited in the claim. Wood et al. teach a control in which the primary antibody is omitted. The stain intensity of this control is subtracted from the stain intensity for the biomarker.

For all of the preceding reasons, applicants maintain that the rejections under §103(a) are misplaced and request that the Examiner reconsider and withdraw these rejections.

Applicants maintain that the claims now pending are in condition for allowance and respectfully request that the Examiner reconsider and withdraw all grounds of objection and rejection and allow the claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Gary J. Gershik 1/24/07

Gary J. Gershik Date
Reg. No. 39,992

EXHIBIT A

Applicants: David L. Rimm et al.
Serial No. 10/062,308
Filed: February 1, 2002

PDR MEDICAL DICTIONARY

SECOND EDITION

PDR®

Medical Dictionary

Applicants: Rimm et al.
Serial No.: 10/062,08
Filed: February 1, 2002
Exhibit A

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...], commissura alba posterior [TA], ventral white col... ventral white c. [TA], commissura ventralis alba...

...ar·ot·o·my (kom'i-sūr-ot'ō-mē). 1. Surgical division ...missure, fibrous band, or ring via an incision or disrup... ...lloon inflation. 2. SYN midline *myelotomy*; ...opening the narrowed mitral orifice for the relief of ...is.

...ment (kō-mit'ment). Legal consignment, by certifica... ...tarily, of an individual to a mental hospital or insti... ...*mitto*, to deliver, consign].

...ce·hi·cle spread. Spread of disease agent from a ... common to those who acquire the disease, e.g., ...ir, syringe contaminated by infectious or noxious ...

... (kō-mō'shē-ō). SYN concussion (2). [L. a moving, ...*commoveo*, pp. *-motus*, to set in motion, agitate]

...SYN brain *concussion*.

...concussion of the retina that may produce a milky ...posterior pole that clears up after a few days.

...ca·ble (kō-mūn'i-kă-bl). Capable of being communi... ...mitted; said especially of disease.

...ous, pl. **com·mu·ni·can·tes** (kō-mū'ni-kans, kō-... ...). Communicating; connecting or joining. [L. pres. ...*nico*, pp. *-atus*, to share with someone, make com...

...ca·tion (kō-mū-ni-kā'shŭn). 1. An opening or con... ...e between two structures. 2. In anatomy, a joining ...said of fibrous, solid structures, e.g., tendons and ...mosis is incorrectly used as a synonym. 3. Infor... ...transmitted from one party to another. [L. *com-*

...production and reception of oral, written, signed, or ...mation among human beings; involves the use of ...n as language received through the auditory, tactile, ...and visual systems and generated through voice ...ting, manual signs, and gestures; c. among humans ...involve the vestibular, olfactory, and gustatory sens...

...SYN total c.

...proach to the education of deaf children that uses a ...sign language, finger spelling, and oral communi... ...o oral auditory *method*, manual visual *method*, ...*ods*, under *method*. SYN simultaneous c.

... (kō-mū'ni-tē). A given segment of a society or a ...

...cenosis.

...a specially structured mental hospital or commu... ...ter milieu that provides an effective environment ...changes in patients through resocialization and ...

...men·tal health cen·ter. A mental health treat... ...ated in a neighborhood catchment area close to the ...nts; introduced in the 1960s via new federal legisla... ...to replace the large state hospitals, which usually ...in remote rural areas; features include offering a ...hensive services by one or more members of the ...ealth professions, provision of continuity of care, ...of consumers in the centers, community location to ...ibility, a combination of indirect or preventive and ..., the use of program-centered as well as case-...ilization, a requirement for program evaluation, and ...s to a variety of health and human services.

...ty (kō-mōr-bid'i-tē). A concomitant but unrelated ...disease process; usually used in epidemiology to ...existence of two or more disease processes. [co- + ...diseased]

...(kom-pak'tă). SYN *stratum compactum*.

...tho·ra·cis (kom-pā'jēz thō-rā'sis). SYN thoracic ...

...scope (kom-par'ă-skōp). A microscope accessory by ...which an observer may directly compare simultaneously the findings in two microscopic preparations. [L. *comparo*, to compare, + G. *skopeō*, to view]

com·par·ti·men·tum. SYN compartment.

c. antebrachii anterius [TA], SYN anterior *compartment* of forearm.

c. antebrachii extensorum, ☆official alternate term for posterior *compartment* of forearm.

c. antebrachii flexorum, ☆official alternate term for anterior *compartment* of forearm.

c. antebrachii posterius [TA], SYN posterior *compartment* of forearm.

c. brachii anterius [TA], SYN anterior *compartment* of arm.

c. brachii extensorum, ☆official alternate term for posterior *compartment* of arm.

c. brachii flexorum [TA], SYN anterior *compartment* of arm.

c. brachii posterius [TA], SYN posterior *compartment* of arm.

c. cruris, SYN lateral *compartment* of leg.

c. cruris anterius [TA], SYN anterior *compartment* of leg.

c. cruris extensorum, ☆official alternate term for anterior *compartment* of leg.

c. cruris fibularium, ☆official alternate term for lateral *compartment* of leg.

c. cruris flexorum, ☆official alternate term for posterior *compartment* of leg.

c. cruris laterale peroneorum [TA], SYN lateral *compartment* of leg.

c. cruris posterius [TA], SYN posterior *compartment* of leg.

c. femoris adductorum, ☆official alternate term for medial *compartment* of thigh.

c. femoris anterius [TA], SYN anterior *compartment* of thigh.

c. femoris extensorum [TA], SYN anterior *compartment* of thigh.

c. femoris flexorum, ☆official alternate term for posterior *compartment* of thigh.

c. femoris mediale [TA], SYN medial *compartment* of thigh.

c. femoris posterius [TA], SYN posterior *compartment* of thigh.

compartment. 1. Partitioned off portion of a larger bound space; a separate section or chamber; the compartments of the limbs are bound deeply by bones and intermuscular septa and superficially by deep fascia and generally are not in communication with the other compartments, and thus infection or increased pathologic pressure may be limited to a compartment; muscles contained within the compartments of the limbs share similar functions and innervation. 2. A separate division; specifically, a structural or biochemical portion of a cell that is separated from the rest of the cell. SYN compartimentum.

adductor c. of thigh, ☆official alternate term for medial c. of thigh.

anterior c. of arm [TA], anterior portion of the space enclosed by the brachial fascia, separated from the posterior c. by the humerus and the lateral and medial intermuscular septa that extend from it; contains muscles that produce flexion, all innervated by the musculocutaneous nerve. SYN compartimentum brachii anterius [TA], compartimentum brachii flexorum [TA], flexor c. of arm☆.

anterior c. of forearm [TA], anterior portion of the space enclosed by the antebrachial fascia, separated from the posterior c. by the radius and ulna and by the intervening interosseous membrane; the spaces are demarcated superficially by the subcutaneous border of the ulna and the (pulse of the) radial artery; contains the pronators of the forearm, flexors of the wrist, and long flexors of the digits, innervated by the median (mostly) and ulnar nerves; is unusual among limb c.'s since it communicates via the carpal tunnel with the midpalmar space. SYN compartimentum antebrachii anterius [TA], compartimentum antebrachii flexorum☆, flexor c. of forearm☆.

anterior c. of leg [TA], anterior portion of space enclosed by the deep fascia of the leg, separated from the posterior c. by the tibia and fibula by the intervening interosseous membrane, and from the lateral c. by the anterior intermuscular septum; contains the dorsiflexors of the foot and long extensors of the toes, all innervated by the deep fibular (peroneal) nerve. SYN compartimentum